U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
PB-285 532

Assessment of the Hazards of Polybrominated Biphenyls

(U.S.) Environmental Protection Agency, Washington, D C

Apr 78

PB 285 532

EPA-560/6-77-037
April 1978

ASSESSMENT OF THE HAZARDS OF POLYBROMINATED BIPHENYLS

by

Frederick J. Di Carlo
Joseph Seifter
Vincent J. DeCarlo

In House Report

Project Officer
Frederick J. Di Carlo

April 1978

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA-560/6-77-037		PB280232

4. TITLE AND SUBTITLE	5. REPORT DATE
Assessment of the Hazards of Polybrominated Biphenyls	April 1978
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
Frederick J. Di Carlo, Joseph Seifter and Vincent J. DeCarlo	
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
OTS IN-HOUSE REPORT	
	11. CONTRACT/GRANT NO.
	IN HOUSE
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
EPA, Office of Toxic Substances Health Review Division, 401 M Street, S.W. Washington, D.C. 20460	14. SPONSORING AGENCY CODE EPA/OTS - TS-792

15. SUPPLEMENTARY NOTES

Project Officer: Frederick J. Di Carlo

16. ABSTRACT

During their peak use period, PBBs represented under 1% of the total sales of fire retardant chemicals, and very probably would have escaped intensive study if the had not been mixed accidentally with animal feed preparations. Instead, international attention was drawn to PBBs by the state-supervised killing of over 35,000 cattle which had been contaminated with PBBs. Interestingly, low doses of PBBs exert a broad spectrum of toxicological, pharmacological, and biochemical effects despite low acute toxicity. These effects and the intensive bioaccumulation of PBBs derive from their structure and their consequent resistance of biotransformation and high solubility in fat. In rodents, PBBs are teratogenic, immunosuppressive, and potentially carcinogenic. In bovine, rodent; and avian species, PBBs reduce feed intake and induce mixed function oxidases of liver microsomes. The latter effect may be responsible for steriod level changes which underline hormonal toxicities observed in cows, mink, rats, and chickens. The effects of PBBs on humans are controversial, but data suggestive of immunological, skin, and liver disorders continue to accumulate. Concern about the clinical effects of PBB's is heightened by the knowledge that these compounds readily enter the fetus by crossing the placental barrier and can be transferred to newborn children after extensive passage into breast milk.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
polybrominated biphenyls PBB's hexabromobiphenyl octabromobiphenyl decabromobiphenyl fire retardants industrial sites air soil water, sediment landfill human exposure FDA guidelines health effects metabolism bioaccumulation		

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
RELEASED UNLIMITED	UNCLASSIFIED	20
	20. SECURITY CLASS *(This page)*	22. PRICE PC A02 MF A01
	UNCLASSIFIED	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

This document is available through the National Technical Information Service (NTIS), 5285 Port Royal Rd, Springfield VA 22161. Telephone: (703) 557-4650.

This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect Environmental Protection Agency views and policies; nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Assessment of the Hazards of Polybrominated Biphenyls

by Frederick J. Di Carlo,* Joseph Seifter,* and Vincent J. DeCarlo*

During their peak use period, PBBs represented under 1% of the total sales of fire retardant chemicals, and very probably would have escaped intensive study if they had not been mixed accidentally with animal feed preparations. Instead, international attention was drawn to PBBs by the state-supervised killing of over 35,000 cattle which had been contaminated with PBBs. Interestingly, low doses of PBBs exert a broad spectrum of toxicological, pharmacological, and biochemical effects despite low acute toxicity. These effects and the intensive bioaccumulation of PBBs derive from their structure and their consequent resistance of biotransformation and high solubility in fat. In rodents, PBBs are teratogenic, immunosuppressive, and potentially carcinogenic. In bovine, rodent, and avian species, PBBs reduce feed intake and induce mixed function oxidases of liver microsomes. The latter effect may be responsible for steroid level changes which underline hormonal toxicities observed in cows, mink, rats, and chickens. The effects of PBBs on humans are controversial, but data suggestive of immunological, skin, and liver disorders continue to accumulate. Concern about the clinical effects of PBBs is heightened by the knowledge that these compounds readily enter the fetus by crossing the placental barrier and can be transferred to newborn children after extensive passage into breast milk.

Introduction

Fire safety legislation during the last decade greatly stimulated the discovery, production, and application of fire retardant chemicals (*1*). By 1975, production of these compounds reached approximately 350×10^6 lb. At present, more than 60% of the total production is used to fireproof carpets and rugs. The balance is impregnated into clothing, home furnishings and a wide variety of construction, electrical and electronic products. PBBs were introduced in 1970, and their manufacture increased 100-fold by 1974 (*2*). Even in 1974, however, the sale of PBBs constituted less than 1% of the total market for fire retardants, because their application was limited predominantly to incorporation into thermoplastics used to construct housings for business machines and electrical units.

In 1973, the accidental addition of 500–1000 lb of PBBs, as FireMaster BP-6, instead of magnesium oxide to animal feed in Michigan resulted in widespread contamination of farm animals requiring the destruction of approximately 29,800 cattle, 5,920 hogs, 1,470 sheep, and 1.5 million chickens (*3*). Also removed from the commercial market were at least 865 tons of animal feed, 17,790 lb of cheese, 2630 lb of butter, 34,000 lb of dry milk products, and nearly 5 million eggs. This mixing error has been alleged to have caused a great number of health problems in people who consumed the milk and food contaminated with PBBs (*4–15*). As a result of this incident, the production of FireMaster BP-6 by Michigan Chemical Corp. was stopped in 1974.

The Environmental Protection Agency has continued to work with the State of Michigan and other Federal Agencies in an effort to bring the PBB problem in Michigan under control. In addition, in early 1977, when information was received on the production of PBBs in New Jersey, an immediate investigation was initiated to determine the level and scope of contamination around the identified manufacturing facilities. This study is currently underway; environmental and human contamination have been found near plants of the Hexcel Corp. in Sayreville, N. J. and White Chemical Co. in Bayonne, N. J. As a consequence of the Michigan incident and the effects of PBBs on animals, the EPA is

* Office of Toxic Substances, U. S. Environmental Protection Agency, Washington, D. C. 20460.

investigating the need for possible regulatory action.

Production of PBBs

Chemistry

The term polybrominated biphenyls (PBBs) refers to a group of chemicals which are formed by substituting bromine for hydrogen in biphenyl. Although theory allows the formation of 209 brominated biphenyls, only about 40 have been synthesized in pure form even on a laboratory scale (*16*).

Commercial PBB products are mixtures. These mixtures contain compounds which differ with regard to both the extent and positions of bromination. For example, 18 different components were detected in commercial FireMaster BP-6 (*17*), although this preparation was commonly identified as "hexabromobiphenyl" by the manufacturer. The quantity of hexabromobiphenyls in BP-6 varied; contents of > 60% (*18*), 63% (*19, 20*), about 75% (*21*), and 90% (*22*) have been reported. It is clear that the major hexabromobiphenyl in BP-6 is the 2,2',4,4',5,5' isomer (*17, 20, 23*). In addition to hexabromobiphenyls, BP-6 contains isomeric tetrabromobiphenyls, pentabromobiphenyls, heptabromobiphenyls, and an octabromobiphenyl (*17, 19, 20*). The major heptabromobiphenyl contains bromine at positions 2,2',3,4,4',5, and 5' (*21*). FireMaster FF-1 (BP-6 mixed with 2% calcium silicate) was found to be contaminated with trace quantities of hexabromonaphthalene, pentabromonaphthalene, and tetrabromonaphthalene (*18, 20*), and with at least 23 other compounds (*20*). Commercial octabromobiphenyl (OBB) contained at least four compounds: a heptabromobiphenyl, isomeric octabromobiphenyls, and a nonabromobiphenyl (*24*). Assays of two samples of OBB showed their chemical composition to be 1.8% heptabromobiphenyl, 45.2% octabromobiphenyl, 47.4% nonabromobiphenyl, and 5.7% decabromobiphenyl (*25*); and 1.0% heptabromobiphenyl, 33.0% octabromobiphenyl, 60.0% nonabromobiphenyl, and 6.0% decabromobiphenyl (*26*). It is noteworthy that the major component of commercial OBB was nonabromobiphenyl, not octabromobiphenyl. Commercial decabromobiphenyl (DBB) was found to consist of 96.8% decabromobiphenyl, 2.9% nonabromobiphenyl, and 0.3% octabromobiphenyl (*27*).

BP-6 is a solid which softens at 72°C and decomposes above 300°C. It is extremely soluble in nonpolar solvents such as toluene and benzene, but dissolves only slightly in water. Its solubility in water has been estimated as 11 ppb (*19*) and 610 ppb (*28*). Upon irradiation with ultraviolet light, 2,2',4,4',5,5'-hexabromobiphenyl in methanol was degraded rapidly to less brominated PBBs and to small quantities of methoxybiphenyls containing 1 to 5 bromine atoms (*29*). Exposing a methanolic solution of BP-6 to ultraviolet irradiation for 45 min converted 70% of the material to pentabromobiphenyl and tetrabromobiphenyl (*30*). OBB dissolved in xylene was also readily photodegraded by reductive debromination (*25*). Further investigation of the photochemical reactivity of PBBs containing 2 to 8 bromine atoms disclosed that debromination proceeds most readily in positions *ortho* to the biphenyl linkage (*31*).

OBB is a solid which melts at 200–250°C and decomposes at 435°C. The solubility of OBB in water was reported as 20–30 ppb (*25*). OBB dissolves readily in organic solvents, but is considerably less soluble than BP-6 (*25*). Commercial decabromobiphenyl is a solid which melts at 380–386°C (*32*).

Assay

The original identification of PBBs in animal feed by Dr. George F. Fries was performed by gas chromatography (*3*), and this type of instrumentation has been used in assay methods which were developed subsequently (*32–35*). The increasingly stringent FDA guidelines for PBBs in foods and animal feeds have been based upon the sensitivity of these methods, not upon toxicological findings (*3*). Electron-capture detectors were employed because they are highly sensitive to halogenated compounds. These detectors have disadvantages, however. One problem is that they are so easily contaminated that their sensitivity becomes variable, and reproducible data can be obtained only by running standards frequently and by intervening with thorough bakeouts. Two noteworthy efforts were made to minimize sample contamination. One involves gel-permeation chromatography as a cleanup procedure for the assay of PBBs in extracts of fat from butter, milk and cheese (*33*). The other method involves cleanup by elution from Florisil columns and was used to determine PBBs in animal feeds (*34*). These procedures can measure PBBs at levels as low as 7 ppb in dairy products and 3 ppb in dry animal feeds. Another problem with electron-capture detectors is that they are difficult to use routinely in conjuction with temperature programming because they require very good temperature isolation between the column and detector and rigorous control of the purity of the carrier gas to preclude the collection of impurities at the head of the column whence they elute and produce poor

baselines. These problems were circumvented in the most sophisticated PBB assay methodology developed to date (*35*). The method involves gas chromatography/mass spectrometry/computer analysis. A wide variety of environmental soil and water samples were assayed for PBBs by using the mass spectrometer in the multiple ion detection mode to attain high sensitivity. This assay system, unlike the others, allowed temperature programming which facilitated the resolution of biphenyls substituted with one to 10 atoms of bromine.

Manufacture

The bromination of biphenyls to PBBs was covered in four patents granted between 1966 and 1974 (*36–39*). Two of the processes involve bromination in the presence of large quantities of chlorine (*36, 39*). The third employs an aluminum halide catalyst (*37*) and the fourth involves using bromine dissolved in chlorosulfonic acid and iodine, aluminum, and iodide–iron mixtures as catalysts (*38*).

The commercial production of PBBs began in 1970. As shown in Table 1, approximately 13.3 million lb of PBBs were produced in the U.S. from 1970 through 1976 (*40*). About 11.8 million lb of this total was hexabromobiphenyl; the remaining 1.5 million lb consisted of octabromobiphenyl and decabromobiphenyl. Michigan Chemical Corp. (St. Louis, Mich.) produced BP-6, and White Chemical Co. (Bayonne, N. J.) and Hexcel Corp. (Sayreville, N. J.) manufactured octabromobiphenyl and decabromobiphenyl. The Michigan Chemical Corp. produced no BP-6 in 1975, but the other two companies continued their production of the more highly brominated biphenyls into 1977. No production figures for 1977 are available, but 1976 production was estimated to consist of 30,000 lb of octabromobiphenyl and 775,000 lb of decabromobiphenyl (*40*).

Import/Export

At present, no PBBs are being imported in commercial quantities. On the other hand, the export of PBBs from the U. S. to Europe has increased during the past several years and totalled 805,000 lb in 1976 (*40*). No information is available on the extent of PBB import in the form of finished plastic products.

Industrial Users

More than 130 companies in the U. S. used PBBs prior to 1976 (*41*). In 1974, the major user of BP-6 was the Borg-Warner Corp, producing flame retardant resins of acrylonitrile, butadiene, and styrene for business machine and electrical housings. At that time, BP-6 was also used in coatings and lacquers and in polyurethane foam for automobile upholstery (*40*). All of these uses were discontinued in late 1974 as a result of knowledge of the Michigan incident. No current users have been identified in the United States.

Pollution from Manufacture and Industrial Users of PBBs

Losses of PBBs to the environment at sites of its manufacture (*40*) can total 51,000 lb/million lb of product through: emission to the air from the vents of the hydrogen bromide recovery system, losses in the waste waters resulting from the quenching and washing of the PBBs as they are recovered from the reaction mass, and solid losses to landfills resulting from drying, handling of the product, shipping and transportation.

Michigan Chemical Corp. discontinued BP-6 production in 1974, and White Chemical Co. and Hexcel Corp. discontinued their OBB and DBB production in early 1977. The following process losses reflect environmental losses that occurred at those plants when PBBs were being produced.

Air

In 1977, the maximum air losses as particulate matter at production sites were estimated to total 1125 lb of PBBs/million lb manufactured (*40*).

In May 1974, air emissions at the Michigan

Table 1. Commercial production of polybrominated biphenyls in the U. S., 1970–1976.

Product	Estimated production, lb							
	1970	1971	1972	1973	1974	1975	1976	1970-1976
Hexabromobiphenyl[a]	20,900	185,000	2,221,000	3,889,000	4,882,000	0	0	11,800,000
Octabromobiphenyl and decabromobiphenyl[b]	31,000	31,000	32,000	359,000	106,000	170,000	805,000	1,544,000
Total PBBs	51,900	216,000	2,253,000	4,248,000	4,988,000	170,000	805,000	13,344,000

[a] Manufactured by Michigan Chemical Corp.

[b] Manufactured by White Chemical Co. and Hexcel Corp. Manufacture was continued in 1977, but production figures are unavailable.

Chemical Corp. showed BP-6 levels of 2-3 × 10^{-6} mg/l. at vents. From these data, the total emission of BP-6 to the air from the vents of the hydrogen bromide recovery system was estimated as 0.07 lb/million lb produced (*19, 40*).

Since PBBs were precipitated from the solvent used during bromination, the reaction mixtures became slurries from which the products were recovered by centrifugation. Particulate PBB was lost to the atmosphere during this centrifugation, but no data are available for the Michigan production site.

After collection by centrifugation, PBBs were dried and pulverized to a fine powder. Dust from this operation was removed by a bag type filter. During May and October 1974, atmospheric levels of BP-6 in the Michigan Chemical Corporation bagger area were 0.016–0.032 mg/l. of air during the bagging operation and 0.003 mg/l. of air after bagging was completed (*41*). Lower levels were detected in other areas of the plant.

Ambient PBBs were not detected in air samples collected downwind from the Hexcel Corp. plant (*42*). However, a New Jersey permit application by this company indicates that some particulate PBBs were lost to the atmosphere during centrifugation and that this loss was less than 0.05% of the product (*43*).

PBBs were detected at the same concentration (6 × 10^{-11} mg/l.) in air samples collected downwind and crosswind from the White Chemical Co. plant (*42*).

Water and Sediment

The losses of PBBs to sewers at manufacturing sites were estimated in 1977 to be only 0.0046 lb/million lb of product (*40*).

In manufacturing PBBs, water was added to the reaction mixture when the desired extent of bromination was achieved. Samples of the Michigan Chemical Corp. effluent discharges were found to contain the highest PBB levels (98–503 ppm) in 1972 (*44*). The company outfalls assayed in 1974 and early 1975 were found to have PBB concentrations as high as 104 ppb, and the total quantity of PBBs then being discharged to the Pine River was estimated as 0.25 lb daily (*44*). Unfiltered Pine River water collected in mid-1974 showed PBB levels of 3.2 ppb and 0.01 ppb in specimens collected 75 yd and 8 miles, respectively, downstream from the plant. The losses of BP-6 to the sanitary sewer system were estimated as 0.0046 lb/million lb of product (*40*).

PBBs reached higher concentrations in stream sediments. Assays conducted from July 1974 to April 1975 showed PBB levels up to 77 ppm in nearshore sediments, and declines in sediment content to 16.2 ppm one-half mile downstream and to 0.1 ppm 24 miles downstream (*44*).

Unfiltered water from an industrial storm sewer at the Hexcel Corp. plant contained 92 ppb, mainly as decabromobiphenyl (*42*). Hexabromo-, octabromo-, and nonabromobiphenyls were also measurable. A swamp containing runoff water from the plant showed the presence of 135 ppb, again predominantly as decabromobiphenyl. Reeds in the swamp contained 25–62 ppm of PBBs, and a turtle captured nearby contained 20 ppb of hexabromobiphenyl.

Liquid effluents from the White Chemical Co. plant were piped to the head of a dead end canal called the Platte Kill. This canal, which acts as a treatment area, empties into the Kill Van Kull River. Unfiltered water from the head of the Platte Kill contained up to 31 ppb of PBBs, while water at the mouth of the canal contained 7 ppb (*42*). Sediment at the head of the Platte Kill contained up to 290 ppm while sediments in the Kill Van Kull contained 20 ppb or less. Interestingly, monobromo- through decabromobiphenyls were found in sediment at the head of the Platte Kill whereas only hexabromo- and heptabromobiphenyls were found in the Kill Van Kull sediment. Fish taken from the Kill Van Kull contained up to 160 ppb of PBBs.

Landfill

A recent estimate of PBB losses as solid waste to landfill was 50,000 lb/million lb of product (*40*).

The Michigan Chemical Corp. reported that their solid waste was approximately 5% of the BP-6 produced and that about half of this waste (269,000 lb) had been deposited in the Gratiot County landfill in St. Louis, Michigan during 1971–1973 (*41*). An investigation of this landfill was initiated in February 1977 (*45*). Groundwater samples were found to contain very low PBB levels (0.1–0.2 ppb), but the concentrations in drainage ditch and catch basin specimens were far greater (0.35–1.2 ppm) (*46*).

Soil

Soil samples from the bagging and loading areas of the Michigan Chemical Corp. contained PBBs at concentrations of 3500 and 2500 ppm, respectively (*44*).

PBBs in soil near the Hexcel Corp. plant ranged from 40 ppb to 3.1 ppm (*42*). Most of the material was decabromobiphenyl, but lower brominated forms down to hexabromobiphenyl were also present.

Soil near the White Chemical Co. plant ranged

from 750 and 2800 ppb in PBBs (*42*). Again, although the decabromo compound was most plentiful, there were significant levels of the less brominated biphenyls down to hexabromobiphenyl.

Human Exposure

Air

Workers involved in the synthesis of PBBs or the manufacture of PBB-containing plastics and plastic products can be exposed to PBBs present in air as vapor or dust.

While PBBs are effective fire retardants in thermoplastics, they can pose a health hazard because flameless combustion of the consumer products (e.g., in a garbage dump or an office fire) causes volatilization of intact PBBs (*47*).

Water

There are no data on the direct exposure of humans to PBB-containing water.

Soil

The useful life of most products containing PBBs has been estimated as 5–10 years, at which time they are discarded or buried in a sanitary landfill (*2, 19*). Adsorption studies show that PBBs are bound tightly by clay minerals (*45*) and various soils (*28*). Thus, PBBs may remain in soil for many years because they are also nonvolatile and resistant to bacterial degradation (*17*).

Nonaccidental Entrance into Food Chain

Grass and carrots grown in PBB-containing soil absorbed very little of the contaminant (*17*), suggesting no hazard from this source. However, the recalcitrance of PBBs to leaching and bacterial degradation indicates that the compounds will be present indefinitely in soils where they can be ingested by farm animals which are used for food.

Accidental Entrance into Food Chain

Through the misuse of PBBs in Michigan, several farms received feeds containing very high levels of the flame retardant. The maximum PBB concentrations ingested by farm animals ranged from 4,000 to 13,500 ppm (*9*). Secondary contamination of animal feed and medicinals occurred through the use of contaminated equipment and facilities. In 1974, 68% of 1770 feed samples collected in Michigan contained PBB residues; 60% in the range of trace to 0.99 ppm, and 8% over 1 ppm (*48*). Resampling in 1975 revealed that 6% of 1208 feed samples were contaminated and that fewer than 0.16% contained more than 1 ppm of PBBs. In 1976, only 0.3% of 663 samples analyzed were contaminated; no samples contained more than 0.1 ppm (*48*). In 1974 and 1975, low level feed contamination with PBBs was detected in Indiana and Illinois (*49*). Contributing to the introduction of PBBs into farm animals was the distribution of contaminated aureomycin by the Farm Bureau; levels of PBBs in their antibiotics were as high as 70 ppm (*50*).

PBB-containing meats, milk, butter, eggs and cheese entered the human food chain before the cause of the Michigan problem was identified. The magnitude of the surveys for PBBs in food is evident from the report that 29,170 products had been assayed as of April 1, 1977 (*51*). In 1974, 14 of 16 milk samples, 4 of 34 butter samples and 11 of 23 cheese samples collected in Michigan were found to exceed FDA guidelines for PBBs (*49*). Another survey showed that 24.9% of 272 finished product samples collected from May to October 1974 were contaminated with PBBs and that 15.8% contained more than 0.3 ppm (*52*). PBBs were detected even in beef in Iowa, duck in Wisconsin, chicken in Alabama, Mississippi, New York and Texas, and turkey in Indiana; the levels were extremely low (*52*).

PBB food levels in Michigan decreased in 1975 (*49*). None of 18 milk samples, 3 of 14 butter samples, and none of 13 cheese samples exceeded FDA guidelines (which had been lowered from 1 ppm to 0.3 ppm on a fat basis) (*53*). Also in 1975, 245 of 2040 meat samples were contaminated with PBBs; 24 contained more than 0.3 ppm (*49*). None of the meat specimens collected in 1976 exceeded FDA guidelines; 96% of 1430 samples were contaminated, but only 1 sample contained more than 0.6 ppm of PBBs (*49*). A market basket survey of meat in 1976 revealed detectable PBBs in only 1 of 102 samples in Michigan (*54*). Outside of Michigan, PBBs were found in 9 of 597 food samples during 1975 and 1976 (*52*).

A recent study (*55*) has confirmed the early impression that PBB levels in dairy products tend to be proportional to their fat content. Additionally, it was found that the spray-drying process apparently exposed and volatilized PBBs from whole and skim milk to reduce PBB levels in the dried products.

On nonquarantined farms, 99% of 74 adults and 97% of 30 children had PBB blood values below 0.019 ppm while, on quarantined farms, only 56% of 82 adults and 29% of 28 children showed levels below 0.019 ppm (*6, 13*). There were 6 adults and 7

children with levels between 0.5 and 2.26 ppm. Levels in fat were consistently higher than those in plasma. The mean concentration in adipose tissue was reported as 1965±356 ppb in quarantined farmers and 516±92 ppb in nonquarantined farmers (5).

Breast milk is rich in fat, and serves as a route of eliminating PBBs. PBB levels are much higher in milk than in blood serum (*13*). The Michigan Department of Public Health conducted studies in 1976 to learn the percentage of women who were passing PBBs into breast milk. Random sampling of 53 women in the lower peninsula showed that 96% of their milk samples contained PBBs; 63% were below 0.1 ppm, 32% were between 0.1 and 1 ppm, and 1 sample was above 1 ppm. Similar sampling of 42 women in the upper peninsula disclosed PBBs in 43% of the specimens; 98% were below 0.1 ppm and 1 sample was between 0.1 and 0.5 ppm (*7*).

In 1976, PBBs were still present in 26 of 28 cultivated fields which had been highly contaminated two years earlier. Additionally, soils where contaminated milk had been dumped contained PBBs at levels up to 1 ppm. Stockpiles of decomposing manure contained abo[illegible]1.5 ppm, and manured garden soils contained up to 0.035 ppm of PBBs (*56*).

PBBs have been identified in the fat of deer, rabbits, coyote, ravens [illegible]nd ducks (*44*, *45*, *57*). They were also found in herring gull eggs at six different Michigan locations on the Great Lakes (*45*) and in fish taken from the Pine River (*44*).

FDA Guidelines for PBB Levels in Food and Animal Feed

In May 1974, the FDA set guidelines of 1.0 ppm of PBB in the fat of milk, meat and poultry, 0.1 ppm in whole eggs and 0.3 ppm in animal feeds. In November 1974, the FDA reduced the guidelines to 0.3 ppm in the fat of milk, meat and poultry, and 0.05 ppm in whole eggs and animal feeds. In July 1977, the Michigan state legislature voted to lower their guidelines for PBBs in cattle to 0.02 ppm, an action which may require the destruction of 34,000 cows (*58*).

Health Effects

Structural Considerations

The physical and chemical characteristics of PBBs favor long periods of residence in living organisms. Their high solubility in fat results in storage in andipose tissues; their chemical stability minimizes change to more water-soluble, more readily excretable molecules; their polarity favors nonspecific adsorption to tissue macromolecules and plasma proteins; their molecular weight favors enterohepatic recirculation; and their polybromination blocks sites where biphenyl would be metabolized by hydroxylation.

Various studies have shown that PBBs concentrate in adipose tissue; they would also be expected to be collected in Kupffer cells of the liver, and perhaps by macrophages. While PBB levels in the body would decline slowly under normal conditions, physiological changes, such as loss of weight, parturition and lactation, would mobilize PBBs from tissue reservoirs with their release into the systemic circulation.

Disposition in Man and Lower Animals

A wide variety of animal species have been found to absorb PBBs. These species include man, cow, pig, dog, mink, guinea pig, rat, mouse, Japanese quail, gull, chicken, and fish. The most definitive quantitative study showed that rats absorbed at least 90% of ^{14}C-labeled 2,2′,4,4′,5,5′-hexabromobiphenyl administered by gavage in doses up to 30 mg/kg even when the material was administered on four consecutive days (*59*). BP-6 blood levels of 2 μg/ml were observed in children and adults on quarantined farms (*6*). Much higher plasma concentrations (*24*–*47* μg/ml) were reached in cows given a single 3-gram dose of encapsulated BP-6 (*60*).

Information on OBB absorption is less clear. A study in rats showed that 62% of a single oral dose of ^{14}C- OBB was eliminated in the feces during the first day (*25*). This finding may indicate that the compound was not completely absorbed.

No information is available on the extent of absorption of DBB.

Studies with radiolabeled PBBs were performed in rats. The levels of radioactivity in adipose tissue, skin, muscle and liver were measured for 6 weeks after intravenous administration of ^{14}C-2,2′,4,-4′,5,5′-hexabromobiphenyl (*59*). After 1 day, muscle contained more than 40% of the isotope and the liver contained more than 10%. These concentrations fell sharply, and at 7 days muscle retained only 5% and the liver less than 2% of the administered radioactivity. Most of this radioactivity was redistributed to the fat, which contained about 25% of the label on day 1 and 60% on day 7. During the subsequent 5 weeks, muscle and liver slowly lost radioactivity while adipose tissue became enriched. The quantity of ^{14}C in skin was within the range of 15–20% of the dose over the entire 6-week period. Similar patterns were observed after the oral administration of radiolabeled 2,2′,4,4′,5,5′-hexabromobiphenyl, indicating that the initial tissue

distribution and subsequent redistribution of this compound are independent of the route of administration (*59*). Another study showed the presence of much higher levels of ^{14}C in fat, adrenal gland, heart and skin than in liver, pancreas and spleen 16 days after administering a single oral dose of ^{14}C- OBB (*25*). When nonradioactive OBB was fed daily to rats, the bromine concentration in the adipose tissue and liver increased steadily, with no plateau during the entire 6 months of the study (*25*). The accumulation of bromine in the fat, liver and muscle of rats was shown to be related to the concentration of OBB in the diet (*61, 62*). Bromine from OBB did not accumulate in rat kidney, skeletal muscle or testis (*25*). There are no data on the tissue distribution of DBB.

A study in laying chickens showed the presence of 12% of the BP-6 does in muscle, 10% in adipose tissue, and 2% in liver (*63*).

A study in Holstein dairy calves indicated that PBB levels in muscle, fat, liver, and kidney increased with the dose (*64*). PBB accumulation in these tissues was especially evident when the dose was increased from 10 mg/kg to 100 mg/kg. A study in lactating cows showed that PBBs entered the bone marrow in a dose-related manner (*65*). PBBs have also been found in the adrenal, brain, heart, kidney, liver, mammary gland, muscle, spleen, and thyroid of cows (*60, 64–67*) and sheep (*66*), in the bile, lung, lymph nodes, ovary, rumen wall, spinal cord, spleen, synovial fluid, testis, thymus, tongue, and uterus of cattle (*60*) and in chicken muscle and liver (*63*).

Humans store PBBs in fat, where concentrations up to 370 (*13*) and 15,000 (*15*) times higher than the blood levels have been reported. A study of 16 men and women, indicated that fat levels of PBB decreased 39% in 6 months (*7*).

PBBs are capable of passing through the placental barrier into the developing fetuses of cows (*68*) and rats (*61, 69*).

The excretion of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl by rats was extremely slow (*59*). After the intravenous administration of a single dose, only 6.6% of the label was excreted in feces over a period of 6 weeks and the total urinary excretion was less than 0.1%. Mathematical extrapolation of the excretion data "indicates that only 9.5% of the total PBB dose would ever be excreted in the feces" (*59*).

OBB was eliminated much faster by rats (*25*). After a single oral dose of ^{14}C- OBB, 65% of the isotope appeared in the feces in 1 day and a total of 73% was excreted in feces in 16 days. The extensive elimination in 24 hr may reflect incomplete absorption.

A pig excreted only 1% of a single intraperitoneal dose of BP-6 in urine and feces in 7 days (*70*).

Approximately 58% of the dose fed to laying chickens was deposited in eggs; 11% was found in excreta (*63*). Gulls also transfer PBB to their eggs (*45*). Cows excrete far more PBB in feces than in urine (*60*); approximately 50% of a single PBB dose was excreted in feces in 7 days and 24% of the dose was excreted with the milk over a period of 95 days.

It is well known that PBBs pass into human milk (*5, 7, 13*), but there are no data on the urinary and fecal excretion of these compounds. Further, there is no information on excretion via the skin; this route may be important for PBBs because lipids (*71*) and halogenated hydrocarbons (*72*) are excreted by glands in the skin, primarily by sebaceous glands associated with hair follicles.

Half-Life and Bioaccumulation

The biological or elimination half-life of a substance is determined from a semilogarithmic plot of the concentration of the substance in blood plasma (on a logarithmic scale) against time (on a linear scale). The plot describes a straight line, and the time required for this concentration at any point on the line to decrease by one-half is the biological half-life. In many cases, plotting tissue levels gives lines with the same slope as the lines obtained from plasma levels. In order to obtain reliable half-life values, studies are performed over periods of four to six half-lives.

Obviously, the repeated exposure of a living organism to a substance with a long half-life results in bioaccumulation.

The most striking study on this topic dealt with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl in the rat, and concluded that "extrapolation of the rate of excretion to infinity indicates that less than 10% of the total dose would ever be excreted" (*59*). Data obtained in a study of ^{14}C- OBB in rats was interpreted to indicate biphasic fecal excretion; the half-life of the first phase was considered to have been less than 24 hr, while the half-life of the second phase was clearly greater than 16 days (*25*). However, one may question the existence of the short half-life phase in the absence of data establishing the complete absorption of OBB by the oral route. This point can be clarified by investigating the excretion of ^{14}C- OBB after intravenous administration. Further, this report on OBB is difficult to reconcile with the observation that bromine levels in the fat of rats dosed with OBB did not decrease during a period of 18 weeks after cessation of dosing (*61, 62*).

PBB excretion in cow milk was observed to be biphasic (*32*). The half-life for the first phase has

been estimated as 10.5 days (*66*) and that for the second phase as 58 days (*67*). Data from another study indicated that cow milk would decrease from 200–400 ppm of BP-6 in fat to 0.3 ppm in 120 weeks (*73*).

Eggs laid by hens after cessation of BP-6 feeding showed decreasing levels of PBBs. From the data, the half-life of PBB elimination by this route was calculated to be 17 days (*63*). A more specific report on this type of PBB elimination placed the half-life of hexabromobiphenyl at 28 days and the half-life of heptabromobiphenyl at 20 days (*74*).

The half-life of PBBs in man has been estimated to be in the order of 10–11 months (*15*), although there are data showing no significant decrease in plasma levels for 5 months (*13*)

The long biological half-life of PBBs in avian, rodent, bovine, and primate species indicates that PBB bioconcentration occurred upon repeated ingestion. It has been amply demonstrated that BP-6 accumulates quickly in fish and that the bioconcentration factor can exceed 10,000 (*2, 24, 44, 75*). However, the bioaccumulation of OBB occurred measurably in rats (*23, 60*), but not in fish (*23*). It is clear that humans experienced the bioconcentration of BP-6 due to storage in fat where concentrations were more than 4000 times the serum levels (*5*).

Biotransformation

PBBs are capable of biotransformations which would yield large numbers of isomeric products. In general, these biotransformations will proceed slowly, but the stereochemistry varies so widely among PBBs that some reactions will proceed much faster than others. The major expected end products would be sulfates, glucuronides, and mercapturic acids. The higher molecular weight metabolites would be excreted slowly due to their entrance into the enterohepatic circulation whereas the lower molecular weight metabolites would be excreted quickly by the kidney.

Definitive work on the biotransformation of PBBs has yet to be done. One publication states that approximately 1% of the BP-6 administered to a pig was excreted as a monohydroxypentabromobiphenyl (*70*). However, it is not clear whether this metabolite was formed from hexabromobiphenyl (by reductive debromination followed by hydroxylation) or directly from pentabromobiphenyl (by hydroxylation). Similarly, there is a single report which suggests the formation of monohydroxydibromobiphenyl in fish (*75*). Another paper implies that fish may debrominate the more highly brominated components of PBB mixtures (*24*). No unconjugated PBBs could be detected in the urine of cows given single 3-gram doses of BP-6 (*60*), and no metabolites of any kind were found in the feces of rats dosed intravenously and orally with radioactive 2,2′,4,4′,5,5′-hexabromobiphenyl (*59*).

Biochemical Pharmacology

PBBs induce oxidative microsomal enzymes in the liver of dogs (*76*), Japanese quail (*77*), adult rats (*27, 69, 78–84*), and neonatal rats (*69, 83*) and in the kidney and mammary gland of maternal rats (*69, 84*). PBBs also induce enzymes in liver cytosol and mitochondria; this was reflected by the elevation of serum levels of glutamic-oxalacetic transaminase (SGOT) in rats (*27*) and cows (*85*), and lactic dehydrogenase in cows (*85*). Additionally, these compounds appear to enhance the catabolism of thyroxine and male sex hormones in cockerels, and of estrogens in hens (*63*) and Japanese quail (*21*). It also appears that PBBs may change the estrogen-progesterone balance in cows (*85, 86*), mink (*87*), and mice (*88*).

Test compounds administered to rodents dosed with BP-6 were cleared more rapidly from plasma and excreted more rapidly in bile (*89–91*). BP-6 decreased the toxicity of ouabain in rats by accelerating the rate of ouabain removal from the blood and liver (*91*). This stimulation of hepatic transport was classified as "a significant drug interaction."

Effects on Animals

Acute Effects. The acute oral LD_{50} of BP-6 has been reported to be approximately 21.5 g/kg for rats (*92, 93*). Although this dose is very high, it is noteworthy that indications of systemic toxicity (such as emaciation) occurred after the oral administration of 10 g/kg (*92*). The acute oral toxicity of OBB is greater than 2 g/kg for rats and greater than 12.5 g/kg for Japanese quail (*61*). The oral LD_{50} of decabromobiphenyl (DBB) is higher than 20 g/kg in the rat (*94*).

BP-6 was more toxic than OBB or DBB when applied to the skin of rabbits. The approximate lethal doses were stated to be 5 g/kg for BP-6 (*95*), greater than 10 g/kg for OBB (*95*) and greater than 8 g/kg for DBB (*94*). Another study placed the acute dermal toxicity of BP-6 in the range of 2.15-10.0 g/kg (*93*).

Rats did not die as the result of inhaling BP-6 dust at a concentration of 71.1 mg/l. of air for 1 hr, but became emaciated after four such exposures (*94*). Rats were unaffected by exposure to OBB dust at a level of 0.96 mg/l. for 4 hr (*26*) and by the inhalation of DBB at a level of 200 mg/l. for 1 hr (*94*).

OBB caused transient irritation of conjunctival

membranes, but not of the cornea, iris, or lens, of the rabbit eye (*27, 94, 95*). BP-6 (*94*) and DBB (*94*) were stated to have no irritative effects on these eye tissues. However, rats exposed to 5 mg of DBB dust/l. air for 6 hr on 5 consecutive days showed mild dyspnea and eye irritation (*27*).

Inspecting the toxicological data shows that PBBs act slowly. In the acute oral toxicity study of BP-6, the first rat to die on the second highest dose (10 g/kg) did so 13 days after dosing (*92*). In the same study, the first rat to die on the highest dose (21.5 g/kg) did so 6 days after dosing and the second rat died on day 9. Deaths were also delayed in the acute dermal toxicity study of BP-6 in rabbits; four of the 15 animals died 5, 7, 8, and 14 days after dosing (*92*). There was a similar finding with DBB; the rabbit which died in the dermal toxicity test did so on day 14 (*94*). One report classified this delayed mortality as "semichronic toxicity" (*96*). This term was used to describe the observation that 500 ppm of BP-6 in the diet of Japanese quail caused deaths in 3 weeks whereas no birds died after receiving a much larger quantity (1 g) as a single oral dose. A similar finding was the death of 37% of chicks fed a diet containing 400 ppm of BP-6 for 15 days (*97*).

The administration of single doses of BP-6 to pregnant rats caused fetal resorption and two teratogenic malformations (cleft palate and diaphragmatic hernia) (*98*). At high doses, the pregnant rodents ate less and their fetuses weighed less than normal. Another important toxic effect from single doses of BP-6 was the formation of liver nodules indicative of potential carcinogenicity in rats (*99*). Administering a single dose of OBB to male rats enlarged the liver and produced changes in its ultrastructure (*100*). A single dose of BP-6 induced mixed function oxidases (MFOs) for prolonged periods in Japanese quail (*77*).

Chronic Effects. The chronic administration of PBBs has been observed to produce a wide variety of biological effects in many animal species. Perhaps the most significant adverse effects were the expression of teratogenicity (cleft palate and exencephaly) in mice (*101, 102*), the suppression of humoral immunity in guinea pigs (*97*), and the suppression of cell-mediated immune mechanisms in mice and rats (*103, 104*).

PBBs adversely affect reproduction by different species. These compounds decrease the comb weight of cockerels (*63, 97*), and decrease the fertility of mink (*87*), hens (*63*), and Japanese quail (*63*). They induce fetal resorption in mice (*88, 105*) and rats (*98*), and abortion in cows (*85, 86*). Additionally, PBBs reduce the survival rate of newborn calves (*88*), mink (*87*), mice (*88*), and chicks (*63*), and reduce the hatchability of avian eggs (*63, 106*).

Other effects of PBBs which have been noted in different species include: reduced feed consumption by cows (*85, 86, 88, 107*), rats (*78, 108*) and chickens (*63, 109*); liver enlargement in cows (*86*), dogs (*76*), rats (*62, 64, 69, 78, 81, 84, 88, 91, 110*), guinea pigs (*97*), mice (*90, 91, 102*), chicks (*63, 97*), and Japanese quail (*21, 63, 96*); increased liver microsomal enzyme activity in dogs (*76*), rats (*69, 78, 79, 82, 89, 107, 110*), mice (*88, 101*), and Japanese quail (*21*); and reduced hematocrit values in chickens (*63*) and rats (*25*). PBBs have also been observed to produce thyroid and testis weight increases in cockerels (*63*), and kidney weight increases in rats (*25*). It is interesting that hyperkeratosis was observed on the eyelids of cows dosed orally with BP-6 (*86*) and on the interior surface of the ears of rabbits after application of the so-called "polar" fraction (*99*). The term "polar" was used in a relative sense; no components of the fraction have been identified.

BP-6 acted synergistically with colchicine to increase the rate of mitosis in rat bone marrow; no chromosomal aberrations were observed (*111*). Other noteworthy effects of BP-6 in rats are reduced adipose tissue weight, elevated plasma cholesterol levels, increased liver lipid and decreased liver RNA (*107*).

Abnormalities in the synthesis of heme result in the formation of large quantities of porphyrin. This disorder, called porphyria, was produced in Japanese quail fed BP-6 (*96, 112, 113*). The accumulation of porphyrins was on a macroscopic scale in the bile, liver, kidney, intestine, and bone of the birds (*96*). The accumulation in the liver was attributed to damage to the mitochondria (*112*).

Minimum Effective Doses. Table 2 shows the lowest doses of PBBs found to have adverse effects in animals. When possible, these doses are expressed as ppm of either commercial hexabromobiphenyl (BP-6) or commercial octabromobiphenyl (OBB) in the diet.

Effects on Humans

It is clear that hundreds of thousands (*116*) if not millions (*117, 118*) of people have ingested food products containing PBBs. It is also clear that man, being at the top of the food chain, has bioconcentrated the very slowly excreted PBBs. The effects of PBBs on human health, however, have been clouded by controversy. Following is an effort to re-evaluate the information from a scientific standpoint aided by recent findings.

The expression, short-term effects, connotes a cause and effect relationship which is measurable within minutes, hours, or days. Review of the available information indicates that there is no informa-

Table 2. Minimum effective doses of PBBs in diet (or by gavage as noted).

	BP-6[a] (Ref.)	OBB[b] (Ref.)
Cows		
Reduced feed intake	5,000 ppm (*85, 88*)	
Decreased body weight	5,000 ppm (*85, 88, 114*)	
Liver enlargement	5,000 ppm (*115*)	
Abortions	5,000 ppm (85[c])	
Reduced progeny survival	10 ppm (*88*)	
Altered heart, respiratory function	5,000 ppm (*88, 114*)	
Severe debilitation, death	5,000 ppm (*88, 114*)	
Kidney, liver, skin pathology	5,000 ppm (*88, 115*)	
Dogs		
Liver enlargement	1 mg/kg (*76*)[c]	
Induced MFOs	1 mg/kg (*76*)[c]	
Mink		
Reduced litter size	1 ppm (*87*)	
Reduced progeny survival	1 ppm (*87*)	
Nursing rats		
Induced MFOs	1 ppm (*88*)	
Rats		
Reduced feed intake	500 ppm (*78*)	
Thyroid enlargement		100 ppm (*25*)
Liver enlargement	5 ppm (*78*)	100 ppm (*25, 61*)
Liver histopathology		100 ppm (*61, 62*)
Induced MFOs	5 ppm (*78, 80, 81*)	
Kidney enlargement		1,000 ppm (*25*)
Reduced fetal weight	100 ppm (*102*)	
Cleft palate in fetus	200 mg/kg (*98*)[c]	
Reduced hematocrit		10,000 ppm (*25*)
Liver nodules	1 g/kg (*99*)[c]	
Immunosuppression	30 mg/kg (*103*)	
Guinea pigs		
Liver enlargement	500 ppm (*97*)	
Mice		
Liver enlargement	50 ppm (*84, 90*)	
Induced MFOs	50 ppm (*84*)	
Reduced progeny survival	200 ppm (*105*)	
Reduced fetal weight	50 ppm (*102*)	
Cleft palate in fetus	50; 1,000 ppm (*101, 102*)	
Exencephaly in fetus	100 ppm (*101, 102*)	
Immunosuppression	30 mg/kg (*103*)	
Nursing mice		
Liver enlargement	50 ppm (*91*)	
Induced MFOs	1 ppm (*88*)	
Hens		
Reduced feed consumption	125 ppm (*63*)	
Reduced egg production	20 ppm (*109*)	
Reduced egg hatchability	10 ppm (*106*)	
Reduced progeny survival	30 ppm (*63*)	
Reduced progeny growth	45 ppm (*63*)	
Chicks		
Reduced weight gain	10 ppm (*106*)	
Reduced body weight	75 ppm (*63*)	
Liver enlargement	50 ppm (*63*)	
Thyroid enlargement	100 ppm (*63*)	
Decreased comb weight	50 ppm (*63*)	
Increased testis weight	200 ppm (*63*)	
Decreased spleen weight	100 ppm (*63*)	
Reduced hematocrit	75 ppm (*63*)	
Reduced hemoglobin	75 ppm (*63*)	
Increased hydropericardium	75 ppm (*63*)	

Table 2 (Continued)

	BP-6[a] (Ref.)	OBB[b] (Ref.)
Japanese quail		
Reduced feed consumption	500 ppm (*21*)	
Reduced egg production	100 ppm (*21*)	
Reduced egg hatchability	100 ppm (*21*)	
Induced MFOs	20 ppm (*21*)	

[a] Commercial hexabromobiphenyl
[b] Commercial octabromobiphenyl.
[c] Administered by gavage.

tion on the effects of PBBs in man within this time frame.

The first effects of PBBs were observed in cattle in September 1973 (*116*) as a result of feeding Farm Bureau pellets purchased during July and fed to the animals in August 1973 (*119*). Another version of the timetable states that sick cows were noticed after one week of feeding the contaminated pellets (*119*). In any case, it is evident that the Michigan Department of Public Health began its study of people exposed to PBBs during the summer of 1974 (*119*) and presented their report on March 19, 1975. Thus, their findings reflect the health of people who ingested PBBs for periods up to 20 months, and cannot be considered to have been short term.

The 189 adults investigated by the Michigan Department of Public Health presented the following list of complaints: numbness, balance problems, nausea, stomach pain, appetite change, weight change, liver trouble, hepatitis, fainting, loss of power, blurred vision, light sensitivity, thyroid trouble, headache, fatigue, irritability, anxiety, depression, pink eye, rash, sores, acne, skin color change, and hair/fingernail change.

After conducting physical examination and laboratory tests, the department concluded: ". . . there has been no consistent pattern of illness or symptoms which occurred excessively in exposed persons."

The preceding conclusion was challenged, and one well-qualified medical research director (*116*) wrote a critique stating that the study was "poorly planned, does not conform to the standards of adequate scientific medical and epidemiological evaluation, was incomplete, probably biased and does not support the conclusions reached and published by the lay press. The study has not been published in the scientific literature, and it probably would not be accepted for publication in a bona-fide scientific journal with a competent and unbiased editorial review board."

A study was made of lymphocytes from 75 New York City residents, 46 Wisconsin dairy farmers and 45 Michigan residents (*120*). With one exception, the lymphocytes of all of the New York and Wisconsin subjects showed normal T and B cell counts and immunological activities. Of the Michigan people, 27 had similarly normal lymphocytes. Lymphocytes from the other 18 Michigan subjects were low in T cells. Further, their T cells contained a high proportion of null (immunologically incompetent) cells. The total number of effective T cells in these 18 people was only 5–10% of normal.

A dermatological study was made of 1029 people from Grand Rapids, Michigan and a control group of 221 people from Wisconsin (*121*). The incidence of halogenacne (21/1029) and of unexplained hair loss (23/1029) in the Michigan group were highly significant because none of the Wisconsin group showed these conditions.

In November 1976, a group of 343 children (ages 0–16) from rural Michigan were studied for possible PBB effects (*122*). In March 1977, 72 children (ages 0–16) from Wisconsin dairy farms were investigated similarly. Rather arbitrarily, the children were divided into three groups; namely, Michigan symptomatic (120), Michigan asymptomatic (223) and Wisconsin asymptomatic (71) groups. The Michigan asymptomatic group differed significantly from the Wisconsin asymptomatic group by greater prevalence of tiredness, decreased appetite and diarrhea. It was concluded that: "There exists a reasonable basis to suspect that ingested PBBs do have acute adverse effects on the health of children" and that "symptoms of ill health can be indistinguishably produced by acute, high-level ingestion and by chronic, low-level ingestion of PBBs."

In five liver function tests, at least five times as many Michigan as Wisconsin residents showed abnormalities (*123*). The incidence of abnormalities in the Michigan group (who had been exposed to PBBs) was 5–11% in the various tests. Abnormal liver function tests had been reported earlier by a private physician treating patients exposed to PBBs (*124*).

Summary

Among the hazardous effects of PBBs on animals are teratogenicity, immunosuppression, and potential carcinogenicity in rodents. Other distinctly untoward effects are hypothyroidism in rats and chickens, testosterone destruction in cockerels, inanition in bovine, rodent, and avian species, and porphyria, reduced egg production, reduced egg hatchability,

and reduced progeny survival in birds. The enlarged livers and high levels of liver enzymes induced by PBBs in bovine, canine, rodent and avian species appear to be relevant to man, but this matter has not been pursued in the clinic.

It is not surprising that the information gained from PBB studies fails to answer a host of important questions and therefore precludes extrapolation of findings in lower species to expectations in man. There are two underlying reasons for this situation. First, commercial PBBs are mixtures of many compounds and these compounds have seldom been studied individually. Thus, it is impossible to draw structure/activity relationships. Indeed, specific toxic effects cannot be assigned to specific molecules. This disadvantage is worsened by the fact that similar chemical compounds may act additively, antagonistically or synergistically. Second, the metabolism of PBBs remains almost totally unknown. This means that the various components of PBBs may be converted to metabolites which are also capable of additive, antagonistic or synergistic activities in different experimental and clinical settings.

The resistance of at least some PBBs to enzymic attack, coupled with their long biological half-life, assures the bioconcentration of these compounds by man. This process of accumulation is now continuing and may produce some manifestation of toxicity at any time, possibly in Michigan residents of some specific genetic description.

The authors are grateful for the competent assistance of Mr. William A. Coniglio, Mr. Thomas Kopp, Ms. Cindy McMillin, Dr. George Parris, and Mr. Michael J. Weaver.

REFERENCES

1. Anderson, E. V. Government rules: Problems, opportunities. Chem. Eng. News, 54: p. 12 (Mar. 22, 1976).
2. Mumma, C. E., and Wallace, D. D. Survey of industrial processing data. Task II—Pollution potential of polybrominated biphenyls. EPA-560/3-75-004, June 1975.
3. Carter, L. J. Michigan's PBB incident: Chemical mix-up leads to disaster. Science 192: 240 (1976).
4. Anonymous. Is PBB a human health hazard? Mich. Med. 75: 560 (1976).
5. Meester, W. D., and McCoy, D. J. Human toxicology of polybrominated biphenyls. Paper presented at Symposium on Environmental Toxicology, Seattle, Washington, Aug. 4, 1976.
6. Isbister, J. L. The short term effects of PBB on health. Michigan Dept. of Public Health report, Feb. 23, 1977.
7. Eyster, J. T. Breast milk studies. Michigan Dept. of Public Health, Nov. 18, 1976.
8. Selikoff, I. J., et al. Health effects of exposure to polybrominated biphenyls. Results of a clinical field survey. Nov. 4-10, 1976. Interim summary report to National Institute of Environmental Health Sciences ES 00928.
9. Kay, K. Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1976. Environmental Res. 13: 74 (1977).
10. Corbett, T. H. The FireMaster incident. In: Cancer and Chemicals. Nelson-Hall, Chicago, 1977, pp. 121-145.
11. Meester, W. D., and McCoy, D. J. Human toxicology of polybrominated biphenyls. Clin. Toxicol. 10: 474 (1977).
12. Wallach, D. P. Livestock poisoning. Chem. Eng. News 55: 43 (July 11, 1977).
13. Humphrey, H. E. B., and Hayner, N. S. Polybrominated biphenyls: An agricultural incident and its consequences. II. An epidemiological investigation of human exposure. Trace Subst. Environ. Health 9: 57 (1975).
14. Anonymous. Polybrominated biphenyls, polychlorinated biphenyls, pentachlorophenyl—and all that. Lancet, 00: 19 (July 2, 1977).
15. Isbister, J. L. PBBs in human health. Clin. Med. 84: 22 (1977).
16. Sundstrom, G., et al. The synthesis and gas chromatographic properties of bromobiphenyls. Sci. Total Environ. 6: 15 (1976).
17. Jacobs, L. W., Chou, S. F., and Tiedje, J. M. Fate of polybrominated biphenyls (PBBs) in soils: Persistence and plant uptake. J. Agr. Food Chem. 24: 1198 (1976).
18. O'Keefe, P. W. Preliminary report. Analysis of environmental samples for trace components from polybrominated biphenyl fire retardants. Presented to the Subcommittee on Conservation and Credit, Committee on Agriculture, United States House of Representatives. April 30, 1976.
19. Kerst, A. F. Polybrominated biphenyls. Technical presentation concerning operations of Michigan Chemical Corporation, St. Louis, Michigan, to Michigan Environmental Review Board, Sept. 23, 1974.
20. Hass, J. R., McConnell, E. E., and Harvan, D. J. Chemical and toxicologic evaluation of FireMaster BP-6. J. Agr. Food Chem. 26: 94 (1978).
21. Babish, J. G., Gutenmann, W. H., and Stoewsand, G. S. Polybrominated biphenyls: tissue distribution and effect on hepatic microsomal enzymes in Japanese quail. J. Agr. Food Chem. 23: 879 (1975).
22. Norstrom, A., Anderson, K., and Rappe, C. Major components of some brominated aromatics used as fire retardants. Chemosphere 4: 255 (1976).
23. Sundström, G., Hutzinger, O., and Safe, S. Identification of 2,2',4,4',5,5'-hexabromobiphenyl as the major component of flame retardant FireMaster BP-6. Chemosphere 5: 11 (1976).
24. Zitko, V. The accumulation of polybrominated biphenyls by fish. Bull. Environ. Contam. Toxicol. 17: 285 (1977).
25. Norris, J. M., et al. Toxicology and environmental factors involved in the selection of decabromodiphenyl oxide as a fire retardant chemical. Appl. Polymer Symp. 22: 195 (1973).
26. Waritz, R. S., et al. Toxicological evaluations of some brominated biphenyls. Am. Ind. Hyg. Assoc. J. 38: 307 (1977).
27. Huntingdon Research Centre. Subacute inhalation toxicity to the rat of Flammex B 10. Jan. 12, 1973.
28. Filonow, A. B., Jacobs, L. W., and Mortland, M. M. Fate of polybrominated biphenyls (PBBs) in soils. Retention of hexabromobiphenyl in four Michigan soils. J. Agr. Food Chem. 24: 1201 (1976).
29. Andersson, K., et al. Photochemical degradation of PCB, PBB and other flame retardants. In: Environmental Quality and Safety, F. Coulston and F. Korte, Eds., Suppl. Vol 111, Georg Thieme Stullgart, 1975, p. 798.
30. Ruzo, L. O., and Zabik, M. J. Polyhalogenated biphenyls. Photolysis of hexabromo and hexachlorobiphenyls. Bull.

Environ. Contam. Toxicol. 13: 181 (1975).
31. Ruzo, L. O., et al. Environmental chemistry of flame retardants. 4. Photodegradation of polybrominated biphenyls (PBB). J. Agr. Food Chem. 24: 1062 (1976).
32. Fries, G. F., and Marrow, G. S. Excretion of polybrominated biphenyls into the milk of cows. J. Dairy Sci. 58: 947 (1975).
33. Fehringer, N. V. Determination of polybrominated biphenyl residues in dairy products. J. Assoc. Off. Anal. Chem. 58: 978 (1975).
34. Fehringer, N. V. Determination of polybrominated biphenyl residues in dry animal feeds. J. Assoc. Off. Anal. Chem. 58: 1206 (1975).
35. Erickson, M. D., Zweidinger, R. A., and Pellizzari, E. D. Analysis of a series of samples of polybrominated biphenyls (PBBs). EPA-560/6-77-020. Aug. 1977.
36. Jenker, H. Process for the production of bromine derivatives of aromatic compounds. U. S. Pat. 3,285,965 assigned to Chemische Fabrik Kalk G. m.b.H., Cologne-Kalk, Germany (Nov. 15, 1966).
37. Mitchell, L. C. Process for production of polybrominated aromatics. U. S. Pat 3,763,248 (assigned to Ethyl Corp.) (Oct. 2, 1973).
38. Fujii, H., and Ohno, I. Highly brominated biphenyls. Japan. Pat. 74-11,689 (assigned to Toyo Soda Mfg. Co., Ltd.) (Mar. 19, 1974).
39. Moore, D. E., Mills, J. F., and Schneider, J. A. Bromination with bromine chloride under pressure. U. S. Pat. 3,845,146 (assigned to Dow Chemical Co.) (Oct. 29, 1974).
40. Neufeld, M. L., Sittenfield, M., and Wolk, K. F. Market input/output studies, task IV: polybrominated biphenyls. EPA-560/6-77-017. Aug. 1977.
41. Kerst, A. F. Letter to D. S. Bryson, EPA Region V. Nov. 11, 1976.
42. Environmental Science and Engineering, Inc. Survey of polybrominated biphenyls (PBBs) near sites of manufacture and use in northeastern New Jersey. EPA Contact No. 68-01-3248. Dec. 1977.
43. Fine Organics, Inc., Subsidiary of Hexcel Corp. Application for certificate to operate control apparatus or equipment. New Jersey State Department of Environmental Protection. Certificate No. CT 20396 (Jan. 29, 1976).
44. Hesse, J. L. Water pollution aspects of polybrominated biphenyl production: results of surveys in the Pine River in the vicinity of St. Louis, Michigan. Presented at the Second National Conference on Complete Water Reuse. Water's Interface with Energy, Air and Solids. Chicago, May 4–8, 1975.
45. Tanner, H. A. Testimony on polybrominated biphenyls, Senate Commerce Committee Hearings, Mar. 30, 1977.
46. Hesse, J. L. Michigan Dept. of Natural Resources. Review of Gratiot County landfill leaching, Mar. 1, 1977.
47. Benbow, A. W., and Cullis, C. F. The formation of toxic products during the combustion of halogen-containing polymer. Eur. Polym. J. 11: 723 (1975).
48. Michigan Department of Agriculture. Feed and ingredient samples tabulation. Enclosure with letter from G. L. Whitehead, Deputy Director, Bureau of Consumer Protection, May 5, 1977.
49. HEW-FDA Division of Chemical Technology. Polybrominated biphenyls in fish, milk, eggs and cheese. Summary report of polybrominated biphenyl findings. 11/10/74 Addendum to FY75 pesticide program (CP 7320.07). April 26, 1977.
50. Michigan Department of Agriculture Laboratory files: Polybrominated biphenyl contamination. June 1977.
51. Whitehead, G. L. Statement on polybrominated biphenyls (PBBs), Science and Space Subcommittee of the U. S. Senate Commerce Committee, Lansing, Michigan, Mar. 31, 1977.
52. Michigan Department of Agriculture. Finished product samples for PBB analysis, May 1974-June 1976. Enclosure with letter from G. L. Whitehead, Deputy Director, Bureau of Consumer Protection, May 5, 1977.
53. USDA, Animal and Plant Health Inspection Service. Meat and poultry inspection program. Objective residue sampling program. Laboratory log sheets from USDA-APHIS Laboratory, 1815 North University, Peoria, Illinois 61604. September/October, 1974.
54. Michigan Department of Agriculture, Food Inspection Division. "Market Basket" meat survey (purchased in Michigan retail stores). Enclosure with letter from G. L. Whitehead, Deputy Director, Bureau of Consumer Protection, May 5, 1977.
55. Murata, T., Zabik, M. E., and Zabik, M. Polybrominated biphenyls in raw milk and processed dairy products. J. Dairy Sci. 60: 516 (1977).
56. Michigan State University. MSU confirms little or no threat from PBB in soils. News release, Department of Information Services, East Lansing, Michigan, Feb. 8, 1977.
57. Fay, L. D. Summary of results of analyses for PBB in wildlife. Memorandum to R. I. Blouch, Michigan Department of Agriculture, Wildlife Pathology Laboratory, Sept. 20, 1976.
58. Anonymous. Michigan lowers action level; Moss plans hearing. Food Chem. News, 19 (18): (July 18, 1977).
59. Matthews, H. B., et al. Distribution and excretion of component of FireMaster BP-6. J. Toxicol. Environ. Health 3: 629 (1977).
60. Willett, L. B., and Irving, H. A. Distribution and clearance of polybrominated biphenyls in cows and calves. J. Dairy Sci. 59: 1429 (1976).
61. Aftosmis, J. G., et al. Toxicology of brominated biphenyls. I. Oral toxicity and embryotoxicity. Toxicol. Appl. Pharmacol. 22: 316 (1972).
62. Lee, K. P., et al. Bromine tissue residues and hepatotoxic effects of octabromobiphenyl in rats. Toxicol. Appl. Pharmacol. 34: 115 (1975).
63. Ringer, R. K., and Polin, D. The biological effects of polybrominated biphenyls in avian species. Fed. Proc. 36: 1894 (1977).
64. Industrial Biotest Laboratories, Inc. Toxicity and tissue residue study with FireMaster FF-1 in dairy calves. IBT No. 651-06733, Nov. 5, 1975.
65. Industrial Biotest Laboratories, Inc. Meat and milk residue study with FireMaster FF-1 in dairy cattle. IBT No. 651-06336, June 7, 1976.
66. Gutenmann, W. H., and Lisk, D. J. Tissue storage and excretion in milk of polybrominated biphenyls in ruminants. J. Agr. Food Chem. 23: 1005 (1975).
67. Fries, G. F., et al. Distribution of polybrominated biphenyl residues in tissues of dairy cattle. J. Dairy Sci. 58: 764 (1975).
68. Detering, C. N., et al. Placental transfer of polybrominated biphenyls by Holstein cows. J. Dairy Sci. 58: 764 (1975).
69. Dent, J. G., et al. Microsomal enzyme induction in maternal liver, kidney, mammary glands and neonatal liver following polybrominated biphenyls. Fed. Proc. 36: 1009 (1977).
70. Kohli, J., and Safe, S. The metabolism of brominated aromatic compounds. Chemosphere 6: 433 (1976).
71. Nicolaides, S. Skin lipids: Their biochemical uniqueness. Science 186: 19 (1974).
72. Matthews, H. B., Domanski, J. J., and Guthrie, F. E. Hair and its associated lipids as an excretory pathway for chlorinated hydrocarbons. Xenobiotica 6: 425 (1976).

73. Detering, C. N., et al. On the rate of excretion of polybrominated biphenyls by lactating Holstein. J. Animal Sci. 41: 265 (1975).
74. Fries, G. F., et al. Retention and excretion of polybrominated biphenyls by hens. Environ. Contam. Toxicol. 15: 278 (1976).
75. Zitko, V., and Hutzinger, O. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. Bull. Environ. Contam. Toxicol. 16: 665 (1976).
76. Farber, T. M., et al. The influence of microsomal induction on serum alkaline phosphatase activity in dogs. Fed. Proc. 35: 376 (1976).
77. Cecil, H. C., Harris, S. J., and Bitman, J. Effects of polychlorinated biphenyls and terphenyls and polybrominated biphenyls on pentobarbital sleeping time of Japanese quail. Arch. Environ. Contam. Toxicol. 3: 183 (1975).
78. Farber, T. M., and Baker, A. Microsomal enzyme induction by hexabromobiphenyl. Toxicol. Appl. Pharmacol. 29: 102 (1974).
79. Dent, J. G., Netter, K. J., and Gibson, J. E. Characterization of various parameters of rat hepatic microsomal mixed function oxidase after induction by polybrominated biphenyls. Toxicol. Appl. Pharmacol. 37: 147 (1976).
80. Dent, J. G., Netter, K. J., and Gibson, J. E. Spectral properties of hepatic cytochrome P-450 induced by polybrominated biphenyls. Arch. Pharmacol. 293 (suppl.); 205 (1976).
81. Dent, J. G., Netter, K. J., and Gibson, J. E. The induction of hepatic microsomal metabolism in rats following acute administration of a mixture of polybrominated biphenyls. Toxicol. Appl. Pharmacol. 38: 237 (1976).
82. Dent, J. G., Netter, K. J., and Gibson, J. E. Effects of chronic administration of polybrominated biphenyls on parameters associated with hepatic drug metabolism. Res. Commun. Chem. Pathol. Pharmacol. 13: 75 (1976).
83. Moore, R. W., Dannan, G., and Aust, S. D. Induction of drug metabolizing enzymes in rats nursing from mothers fed polybrominated biphenyls. Fed. Proc. 35: 709 (1976).
84. Dent, J. G., Cagen, S. Z., and McCormack, K. M. Liver and mammary arylhydrocarbon hydroxylase and epoxide hydratase in lactating rats fed polybrominated biphenyls. Life Sci. 20: 2075 (1977).
85. Moorhead, P. D., et al. Pathology of experimentally induced polybrominated biphenyl toxicosis in pregnant heifers. J. Amer. Vet. Med. Assoc. 170: 307 (1977).
86. Jackson, T. F., and Halbert, F. L. Toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle. J. Amer. Vet. Med. Assoc. 165: 437 (1974).
87. Michigan Science in Action. MSU research on PBBs. Michigan State University Agricultural Experimental Station. May 1976.
88. PBB Scientific Advisory Panel Report to William G. Millken, Governor, State of Michigan, May 24, 1976.
89. Cagen, S. Z., and Gibson, J. E. Stimulation of biliary function following polybrominated biphenyls. Toxicol. Appl. Pharmacol. 41: 147 (1977).
90. Cagen, S. Z., Preache, M. M., and Gibson, J. E. Enhanced disappearance of drugs from plasma following polybrominated biphenyls. Toxicol. Appl. Pharmacol. 40: 317 (1977).
91. Cagen, S. Z., and Gibson, J. E. Ouabain lethality as a measure of biliary function in developing mice and rats and effect of polybrominated biphenyls. Toxicol. Appl. Pharmacol. 40: 327 (1977).
92. Hill Top Research, Inc. Acute toxicity and irritation studies with FireMaster BP-6 hexabromobiphenyl. 1970.
93. Anonymous. FireMaster BP-6. A new flame retardant additive from Michigan Chemical Corp. Second revision. April 26, 1971.
94. Consumer Product Testing Co., Inc. Final report to Hexcel-Fine Organics. Mar. 10, 1977.
95. Aftomis, J. G., et al. Toxicology of brominated biphenyls. II. Skin, eye, and an acute test method for evaluating hepatotoxicity and accumulation in body fat. Toxicol. Appl. Pharmacol. 22: 316 (1972).
96. Strik, J.J.T.W.A. Toxicity of hexachlorobenzene (HCB) and hexabromobiphenyl (HBB). Med. Fac. Landbouwwetensch. 38: 709 (1973).
97. Vos, J. G., and van Gendern, H. Toxicological aspects of immunosuppression. In: Pesticides and the Environment, W. B. Deichmann, Ed. Intercontinental Medical Book Corp., New York, 1973, pp. 527–545.
98. Beaudoin, A. R. Teratogenicity of polybrominated biphenyls in rats. Environ. Res. 14: 81 (1977).
99. Kimbrough, R. D., et al. Toxicity of polybrominated biphenyl, FF-1 in rats and rabbits: persistence, hepatic porphyria, hepatic neoplasia, hyperkeratosis. Lancet, 8038: 602 (Sept. 17, 1977).
100. Lee, K. P., et al. Octabromobiphenyl-induced ultrastructural changes in rat liver. Arch. Environ. Health 30: 465 (1975).
101. Corbett, T. H., Beaudoin, A. R., and Cornell, R. G. Teratogenicity of polybrominated biphenyls. Teratology 11: 15A (1975).
102. Corbett, T. H., et al. Toxicity of polybrominated biphenyls (FireMaster BP-6) in rodents. Environ. Res. 10: 390 (1975).
103. Luster, M. Effects of PBBs on immunocompetence in laboratory animals. Presentation to DHEW Committee to Coordinate Toxicology and Related Programs, NIH, July 26, 1977.
104. Moore, J. A. Testimony before House of Representatives Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce, Washington, D. C., Aug. 2, 1977.
105. Preache, M. M., Cagen, S. Z., and Gibson, J. E. Perinatal toxicity in mice following maternal dietary exposure to polybrominated biphenyls. Toxicol. Appl. Pharmacol. 37: 171 (1976).
106. Lillis, R. J., et al. Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci. 54: 1550 (1975).
107. Prewitt, L. R., Cook, R. M., and Fries, G. F. Field observations of Michigan dairy cattle contaminated with polybrominated biphenyl. J. Dairy Sci. 58: 763 (1975).
108. Garthoff, L. H., et al. Biochemical and cytogenic effects in rats caused by short-term ingestion of Aroclor 1254 or FireMaster BP-6. J. Toxicol. Environ. Health 3: 1 (1977).
109. Cecil, H. C., and Bitman, J. Toxicity of polybrominated biphenyl and its effects on reproduction of White Leghorn hens. Paper presented to section of Pesticides Chemistry, 190th Natl. Mtg., American Chemical Society, August 1975, paper 122.
110. Babish, J. G., Stoewsand, G. S., and Lisk, D. J. Induction of tissue microsomal enzymes and polybrominated biphenyl metabolism in Brassica fed rats. Fed. Proc. 35: 376 (1976).
111. Ficsor, G., and Wertz, G. F. Polybrominated biphenyl non teratogenic, c-mitosis synergist in rat. Mutation Res. 38: 388 (1976).
112. Strik, J.J.T.W.A. Chemical porphyria in Japanese quail (*Coturniz c. Japonica*). Enzyme 16: 221 (1973).
113. Strik, J.J.T.W.A. Species differences in experimental porphyria caused by polyhalogenated aromatic compounds. Enzyme 16: 224 (1973).
114. Irving, H. A., et al. The effects of polybrominated biphenyls on growth, feed intake, and health of pregnant heifers. Paper presented at meeting of American Dairy Science Association, Raleigh, N. C., June 1976.

115. Willett, L. B., et al. The effects of polybrominated biphenyls on body organs and changes in blood and urine chemistry of pregnant heifers. Paper presented at meeting of American Dairy Science Association, Raleigh, N. C., June 1976.
116. Stadtfeld, C. K. Cheap chemicals and dumb luck. Audubon, Jan. 1976, p. 110.
117. Halbert, F. Testimony before Senate Subcommittee on Health. April 8, 1976.
118. McGuire, A. Statement before House of Representatives Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce. Washington, D. C., Aug. 2, 1977.
119. Senate Special Investigating Committee on Polybrominated Biphenyls. The contamination crisis in Michigan. July, 1975.
120. Bekesi, J. G. Testimony before House of Representatives Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce, Washington, D. C., Aug. 2, 1977.
121. Chanda, J. Testimony before House of Representatives Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce, Washington, D. C., Aug. 2, 1977.
122. Barr, M., Jr. Testimony before House of Representatives Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce, Washington, D. C., Aug. 2, 1977.
123. Salvati, D. T. Letter to Representative D. Albosta, Mar. 4, 1975. In: Senate Special Investigating Committee on Polybrominated Biphenyls. The contamination crisis in Michigan. July 1975.